PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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EINGEGANGEN
29. März 2006
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WV : 29/5/06/a
Frist 28.06.2006/SS/07

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/003371	31.03.2005	31.03.2004

International Patent Classification (IPC) or both national classification and IPC
C07K16/28, C12N5/20, G01N33/577, G01N33/53, C07K14/705

Applicant
ADNAGEN AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/003371

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5
	No:	Claims	1-4, 6-16
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-16
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Re Item V Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: Huie et al: "Antibodies to human fetal erythroid cells from a nonimmune phage antibody library" Proceedings of the National Academy of Sciences, vol. 98(5), 2001-02-27, pages 2682-2687, XP002974719;

D2: Alvarez et al: "Development, characterization, and use of monoclonal antibodies made to antigens expressed on the surface of fetal nucleated red blood cells" Clinical Chemistry, vol. 45(9), 1999-09, pages 1614-1620, XP002365991.

Document D1 discloses the isolation and characterization of monoclonal antibodies to human fetal erythroid cells from a non immune phage antibody library which react specifically with fetal nucleated red blood cells (NRBC) and do not react with adult white blood cells and red blood cells (p. 2684. left-hand column, § 2, 3). The generated antibodies react with antigens other than CD71, CD36 and I/i and might be useful for prenatal diagnosis and treatment of polycythemia or erythroleukemia (p. 2687, right-hand column, l. 13-21). The antibodies are used to detect and identify fetal cells in a sample by flow cytometry or immunohistochemistry and immunofluorescence. The use of the generated antibodies for isolating NRBCs from maternal blood is suggested (abstract).

Document D2 discloses the production of monoclonal antibodies specific for NRBC (CD71+, CD45-) which to not bind to adult red blood cells (p. 1618, right-hand column, § 3). The antigen recognised is CD71 at two different conformational epitopes by the different antibodies. The antibodies are used to isolate NRBC by immunomagnetic separation from maternal blood (p. 1616, left-hand column, § 2) in order to use the isolated fetal cells for assessing genetic disorders (p. 1619, left-hand column, § 4).

1 **NOVELTY**

1.1 In view of the disclosure of documents D1 & D2, each one individually, the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-4, 6-16 is not new in the sense of Article 33(2) PCT.

1.2 None of the cited prior art document discloses the hybridoma cell deposited under accession number DSM ACC 2666. Hence, claim 5 is new and meets the requirements

of Art. 33(2) PCT.

2 INVENTIVE STEP

2.1 Document D1 is regarded as being the closest prior art for the subject-matter of claim 5, and discloses the isolation and characterization of monoclonal antibodies to human fetal erythroid cells from a non immune phage antibody library, which react specifically with fetal NRBC and do not react with adult white blood cells and RBC (p. 2684. left-hand column, § 2, 3). The generated antibodies react with fetal red blood cell antigens other than CD71, CD36 and I/i.

2.2 The subject-matter of claim 5 therefore differs from this known D1 in that the antibody binding to fetal NRBC and not adult RBC is produced by an hybridoma, which is claimed and not by a phage library. There is no effect associated with the difference.

2.3 The problem to be solved by the present invention may therefore be regarded as the provision of alternative means to produce an antibody binding to fetal NRBC and not adult RBC.

2.4 The proposed solution is the hybridoma deposited with accession number DSM ACC 2666, which produces an antibody binding to fetal NRBC and not adult RBC. This solution cannot be considered as involving an inventive step (Article 33(3) PCT) since it is standard procedure to produce antibodies having same properties by an alternative well known method (hybridoma technic vs phage display library).

Re Item VII Certain defects in the international application

1 Claim 1 refers to a monoclonal antibody reacting with a surface antigen present **on** fetal red blood cells **including** their nucleated precursor. It is unclear (Art. 6 PCT) if the antigen is recognized only when present on cell surface or also when isolated. Furthermore, it is unclear if the nucleated precursor are part of the fetal red blood cells, in which case it is redondant to mention them, or if they are a different group of cells, which are recognised. Hence, claim 1 does not meet the requirement of clarity of Art. 6 PCT.

2 Claims 1-3 try to define the matter for which protection is sought by negative features (not binding to adult erythroid cells, cells not expressing CD45). This leads to doubt concerning the matter for which protection is sought (antibody), thereby rendering the claims unclear, Art. 6 PCT.

3 The relative term "most cells" used in claim 2 is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim unclear, Arti. 6 PCT.

4 Claim 3 relates to an antibody reacting with fetal NRBC and not adult ones and does not bind to CD71. However, in present application (p. 11, l. -34) the antibody (4B8) is shown not to compete with an anti CD71 antibody used. This only means that they do not recognise the same epitope and not that the generated antibody does not bind to CD71 in general. Hence, claim 3 lacks support and does not meet the requirements of Art. 6 PCT. Furthermore, the claim attempts to define the subject-matter in terms of the result to be achieved (not binding to CD71), which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

5 Claims 6 & 8 appear to relate effectively to the same subject-matter with claims 4 & 5 and 7 & 1-3, to which they respectively refer and differ from them only with regard to the definition of the subject-matter for which protection is sought. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.

6 Claim 9 refers to a surface antigen of fetal red blood cells. No such antigen was isolated or characterized by present application and the antigen is only defined by a desired property (namely, binding of a monoclonal antibody) without providing the technical features which would allow to differentiate it from the prior art. Hence, claim 9 does not meet the requirements of Art. 6 PCT.

7 Claim 15 refers to the use of a method according to claims 13 or 14 for the detection of anomalies in fetal cells detected and identified by the method of claims 13-14. However, the method of claims 13-14 is a method for detection or identification of fetal cells and not of detection of genetic anomalies in said cells. Therefore, claim 15 does not meet the requirements of Art. 6 PCT because the scope for which protection is sought is not clearly defined.